
بسم الله الرحمن الرحيم
السلام عليكم ورحمة الله وبركاته



Armed Forces College of Medicine

AFCM



Analgesic Antipyretics (1)

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INTENDED LEARNING OBJECTIVES (ILO)

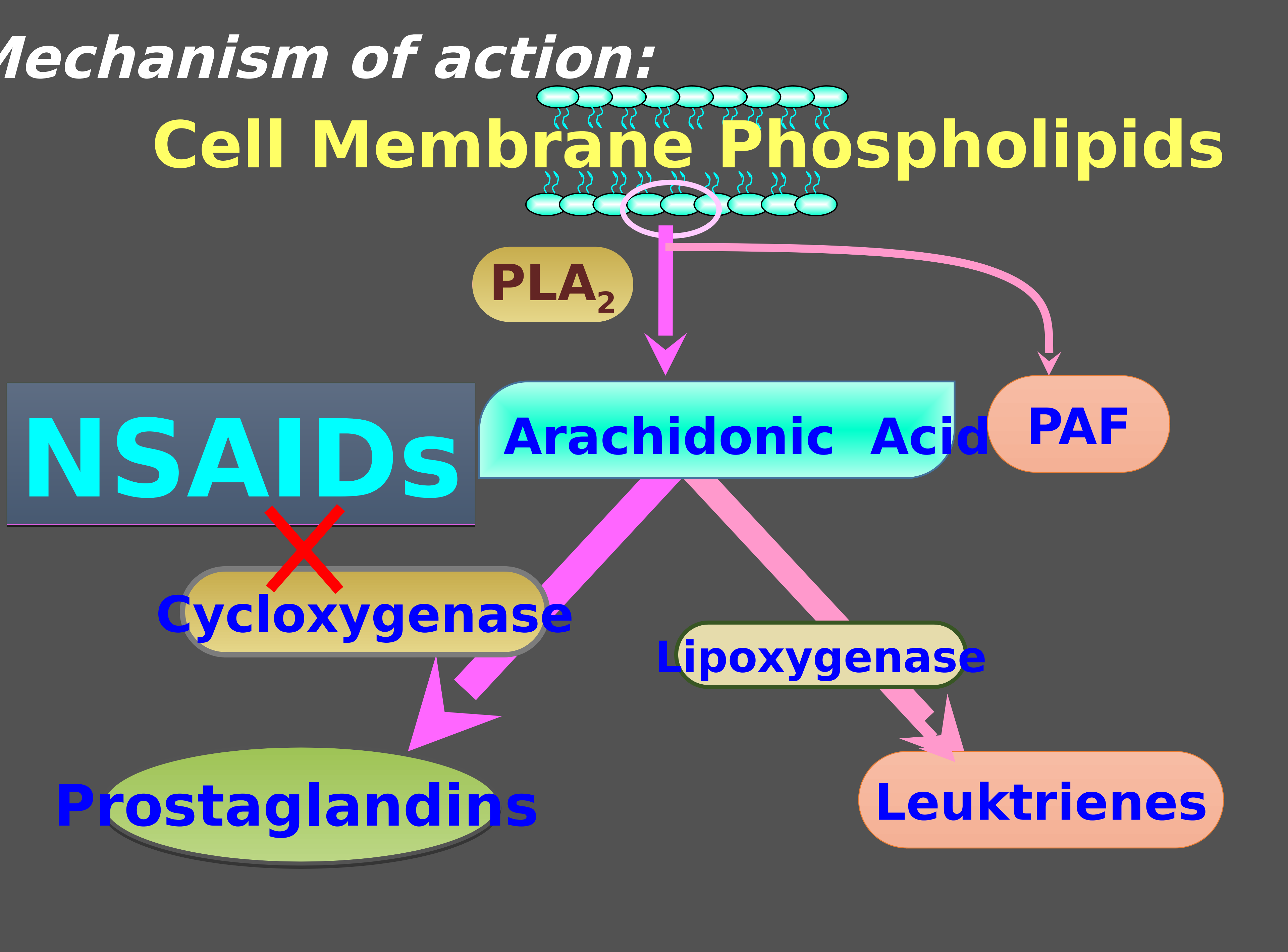
By the end of this lecture the student will be able to:

1. Explain the mechanism of analgesic, antipyretic and anti-inflammatory actions of Aspirin as a prototype of nonsteroidal anti-inflammatory drugs (NSAIDs).
2. Identify the therapeutic uses of Aspirin

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

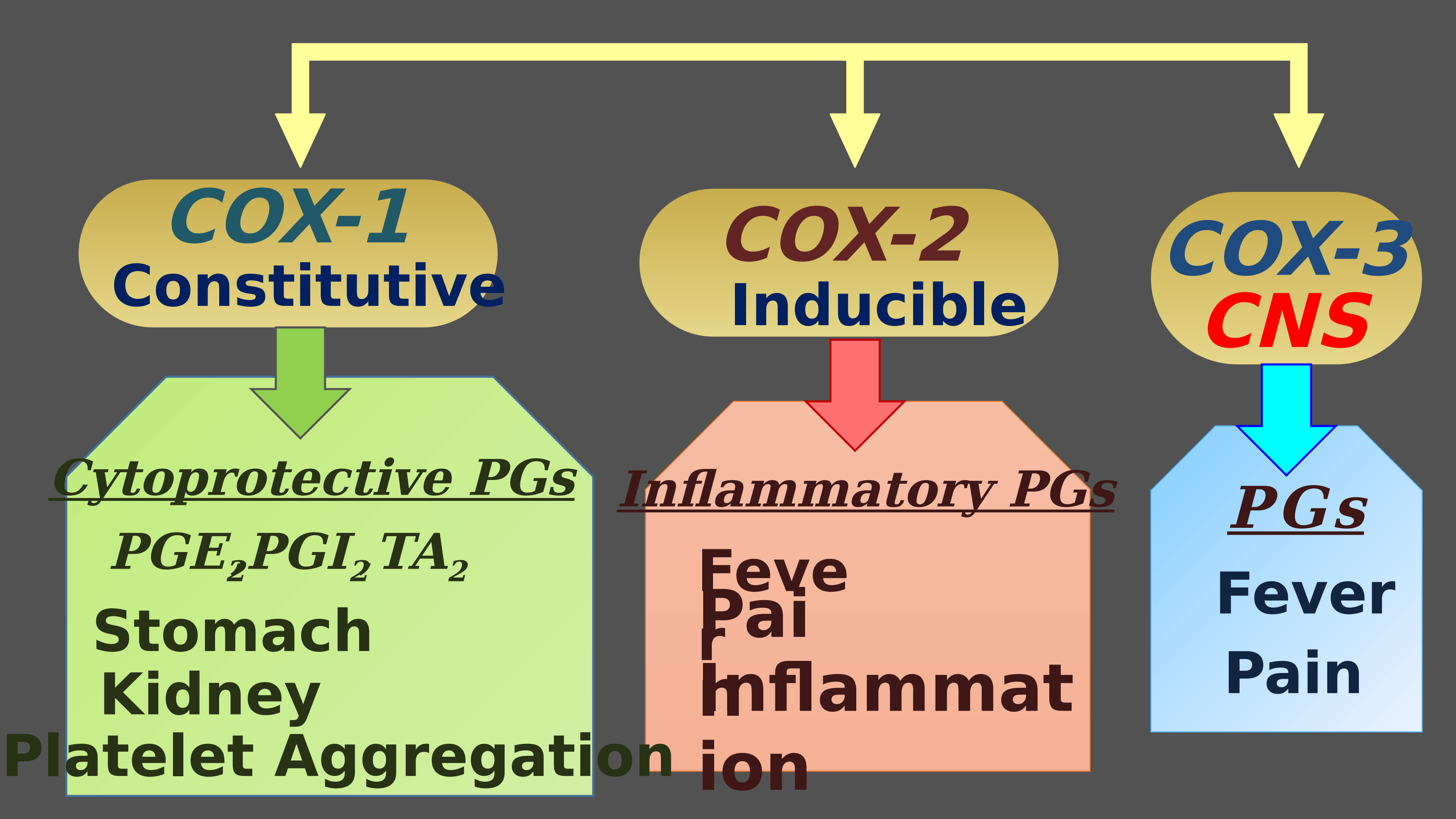
They are group of drugs which have:

- **Analgesic effect**
- **Anti-Pyretic effect**
- **Anti-Inflammatory**



Mechanism of action:
Cell Membrane Phospholipids
PLA2
Arachidonic Acid
PAF
NSAIDs
Cycloxygenase
Lipoxygenase
Prostaglandins
Leuktrienes

Cycloxygenase
COX

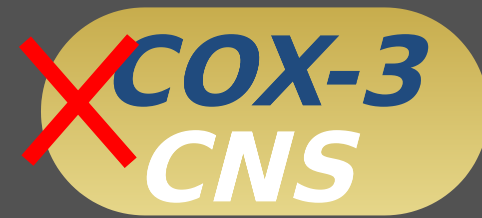


Cycloxygenase COX

1. Non-Selective COX inhibitors







Cytoprotective PGs

PGE_2, PGI_2, TA_2

Stomach
Kidney
Platelet Aggregation

GIT irritation
Nephropathy
Bleeding tendenc

Main Adverse Effects

Inflammatory PGs

Pain
Fever
Inflammation

Analgesic
Anti-Pyretic
Anti-Inflammatory

PGs

Pain
Fever

Analgesic
Anti-Pyreti

Main Uses





Cytoprotective PGs

PGE_2, PGI_2, TA_2

G.I.T. Irritation

Nephropathy

Bleeding tendency

Celecoxib

2. Selective *COX-2*

Inflammatory PGs

Analgesic

Anti-Pyretic

Anti-Inflammatory

Acetaminophen (Paracetamol)

3. Selective *COX-3*

Analgesic

Anti-Pyretic

Salicylates

Derived from Salicylic acid

They Include

- Acetyl-salicylic acid (Aspirin)
- Methyl Salicylate

<u>Mechanism of action</u>:

- *Aspirin* is a weak organic acid that **irreversibly acetylates** (and, thus, inactivates) **cyclooxygenase**
- The **other NSAIDs**, are all **reversible** inhibitors of cyclooxygenase.
- Aspirin (acetylsalicylic acid) blocks the cyclooxygenase pathway by **inhibiting COX1 and COX2 (non selective)**
- This results in **↓ PGs, prostacyclin and thromboxane**.

Mechanism of action

Salicylates

COOH

OH C CH$_3$

O

Acetylsalicylic acid (Aspirin)

Salicylic acid

COX

Irreversible acetylation

(Inactive COX enzyme)

Inhibition of PGs synthesis

To regain activity

COX

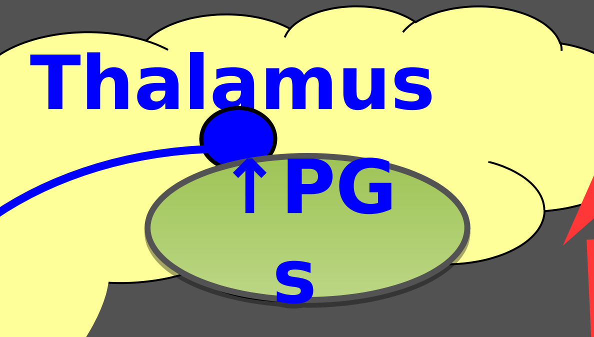
Can be re-synthesized by all cells except platelets?!

A. Analgesic action:

- **PGE2** is thought to **sensitize nerve endings** to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process.
- Thus, **by decreasing PGE2 synthesis**, *aspirin and other NSAIDs* ***repress the sensation*** **of pain peripherally & centrally (↓ the pain transmission at subcortical sites –Thalamus-)**
- The salicylates are used mainly for the **management of pain of low to moderate intensity** arising from musculoskeletal disorders rather than that arising from the viscera.

Salicylates

Analgesics



Salicylates

Pain threshold perception

Sensitivity of the nerve endings to the action of chemical mediators



s

Inflammation

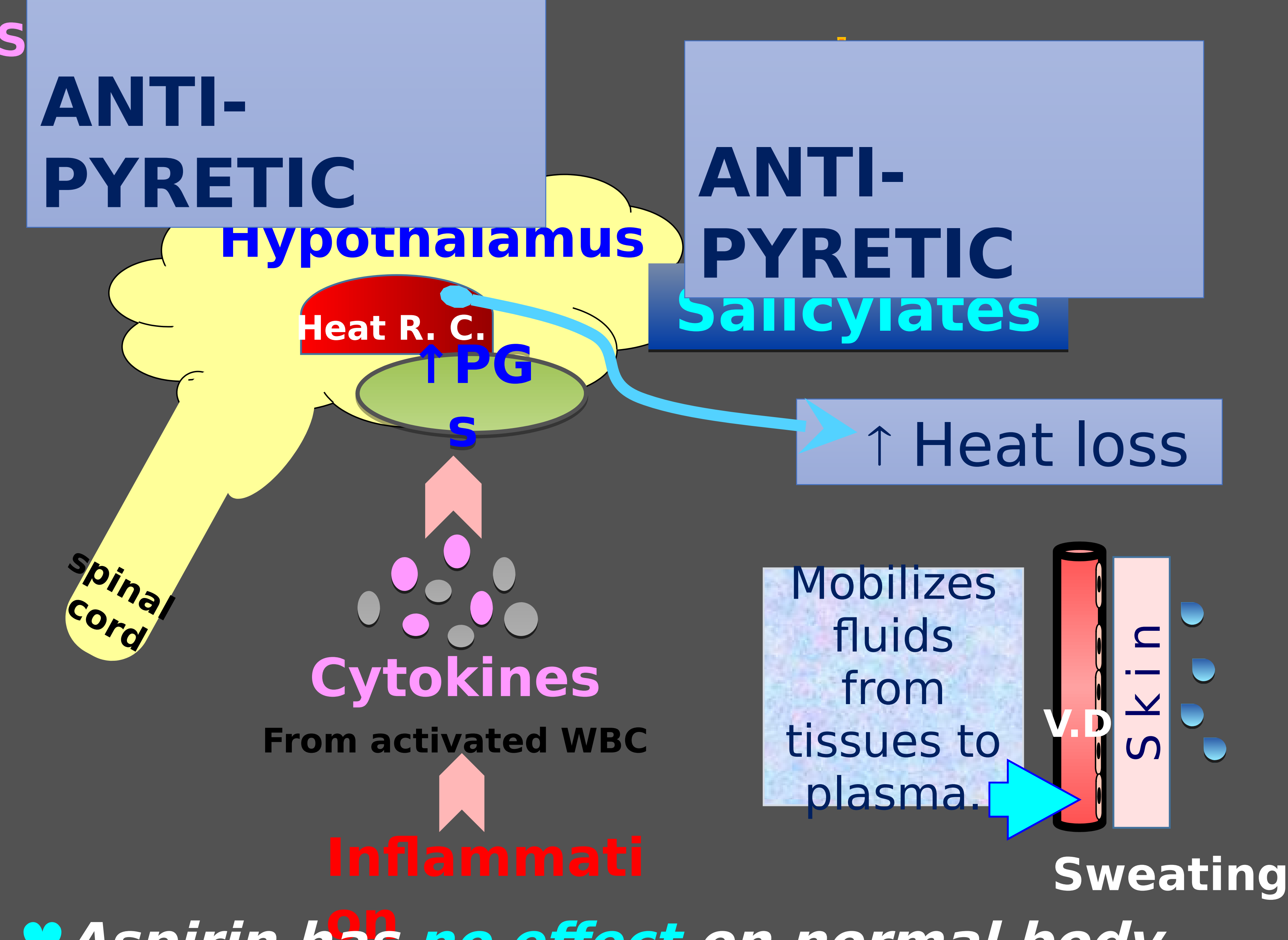
Spinal cord

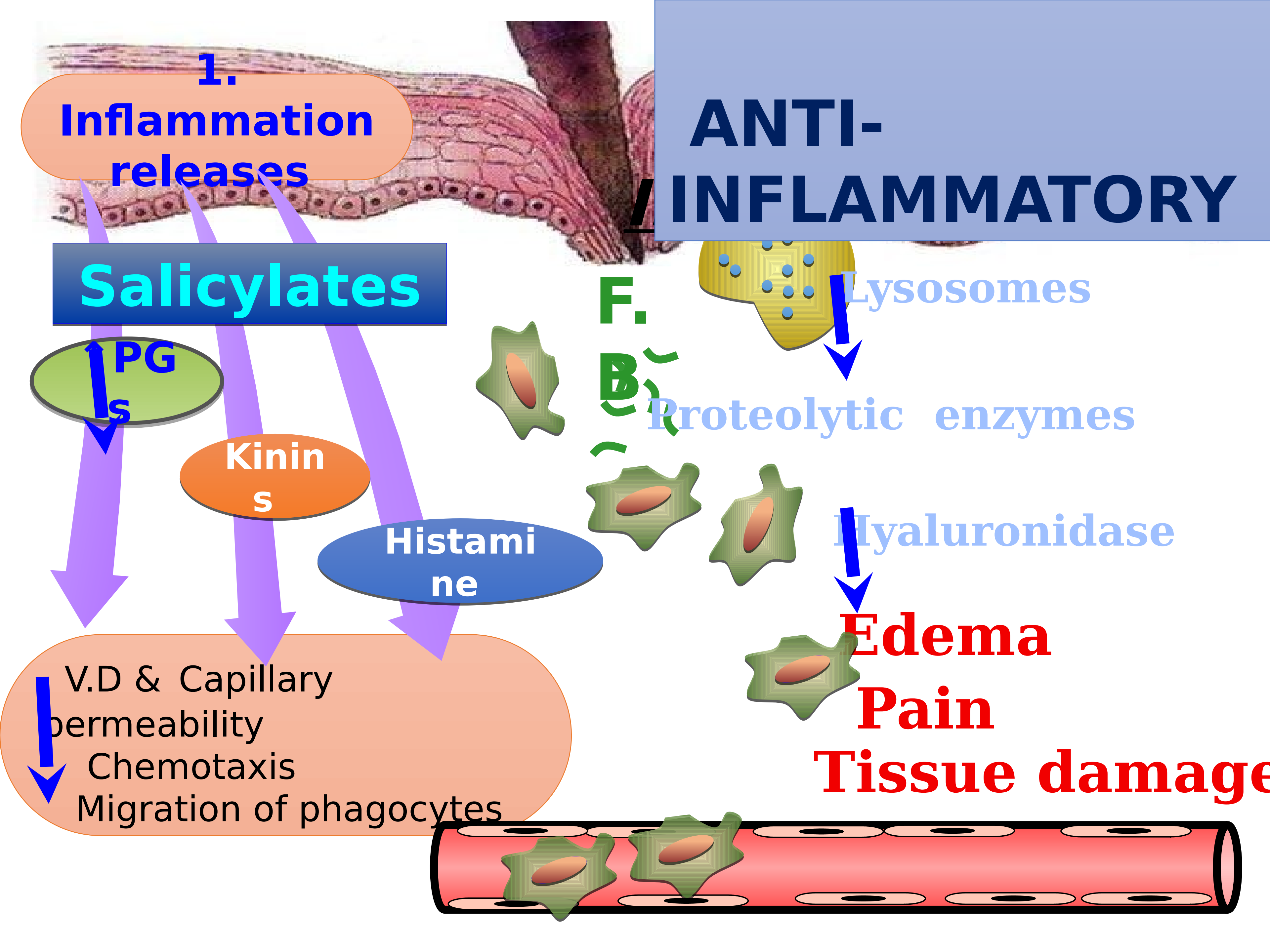
Analgesia

Chemical mediators

b. Antipyretic action:

- Salicylates **lower body temperature** in patients with fever **by inhibiting PGE2 synthesis and release.**
- *Aspirin and other NSAIDs* ***reset*** **the “thermostat” in CNS** toward normal. This rapidly **lowers the body temperature** of febrile patients by increasing heat loss as a result of **peripheral vasodilation and sweating.**


ANTI-PYRETIC
ANTI-PYRETIC
Hypothalamus
Heat R. C.
↑PGs
Salicylates
↑ Heat loss
spinal cord
Cytokines
From activated WBC
Inflammation
Mobilizes fluids from tissues to plasma.
V.D
Skin
Sweating
♥Aspirin has no effect on normal body


ANTI-INFLAMMATORY
1. Inflammation releases
Salicylates
PGs
Kinins
Histamine
F. B
Lysosomes
Proteolytic enzymes
Hyaluronidase
Edema
Pain
Tissue damage
V.D & Capillary permeability
Chemotaxis
Migration of phagocytes

Salicylates -

ANTI-INFLAMMATORY

↓PG synthesis

V.D & Capillary permeability

Chemotaxis

Migration of phagocytes

↓Pain

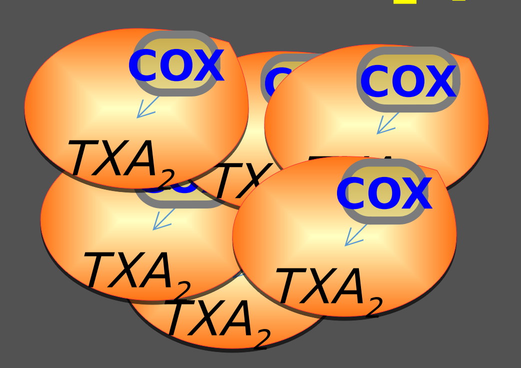
↓V.D.

↓Edema

Salicylates - actions

Blood: Small dose of Aspirin (75 – 150 mg)

Selective & Irreversible inhibition of TXA_2 production



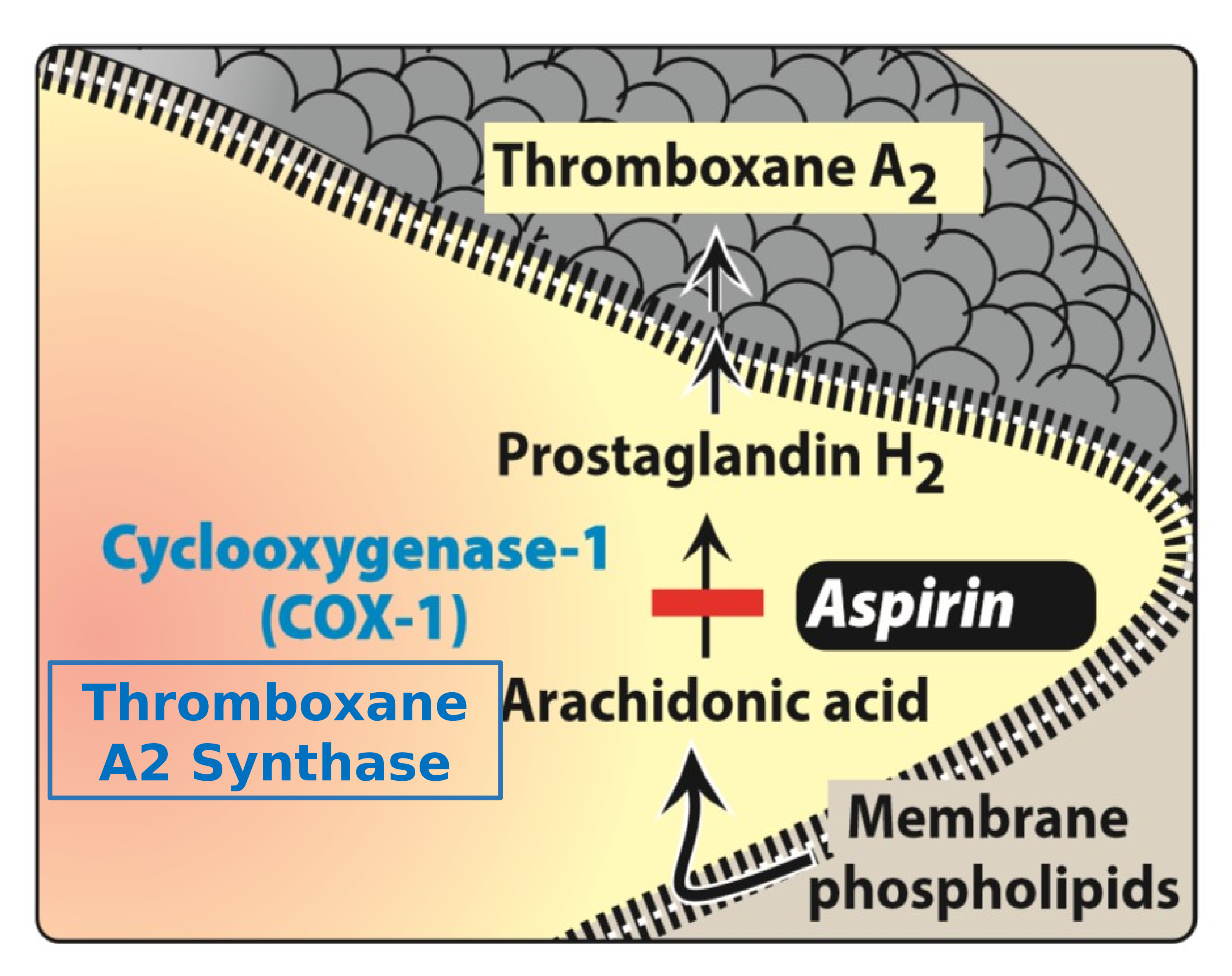
Inhibit platelet aggregation

This action lasts for about one week ?!

Stop aspirin one week before surgery

Platelet has no nucleus → Platelet can not regenerate cox or synthesize TXA_2

- The action of aspirin on platelets last for platelets re-



Aspirin irreversibly inhibits platelet
cyclooxygenase

The common mechanism of action of NSAIDs is inhibition of the following enzyme:

a) Cholinesterase
b) Cyclo-oxygenase
c) Lipo-oxygenase
d) Phosphodiesterase
e) Phospholipase

Aspirin - Therapeutic Uses

Systemic uses

1) **Antiplatelet** (inhibit platelet aggregation)

Aspirin Low dose (75-150 mg/day)

Prophylaxis in:

- **Transient ischemic attacks (TIAs)**
- **In patients with previous stroke**
- **Angina pectoris (chronic stable &**

Intermediate Dose :

325 mg tablet (1- 2 tablet/ 6 hours)

2) Analgesic:

in Mild to moderate superficial pain

- Headache,toothache,myalgia, dysmenorrhea

- Mild to moderate pain 2ry to inflammation

3) Anti-pyretic:

- Fever

4) Anti-Inflammatory

High dose > 4 gm /day

Treatment of inflammation e.g:

1- Osteoarthritis

2- Gout

3- Rheumatoid arthritis



- It does not arrest the progress of the disease or induce remission.

4- Rheumatic fever:

✓ Relieve Arthritis

Salicylates - Therapeutic Uses

B) Local Uses:

1- **Salicylic acid:** Keratolytic in acne ,corns & warts

2- **Methyl-Salicylate** Counter-irritant in Arthritis & Myositis.
(As in arthritis cream and sports rubs)

Aspirin in an oral dose of > 4 gm /day is used in which of the following therapeutic uses?

a) Keratolytic
b) Analgesic
c) Antipyretic
d) Anti-inflammatory
e) Antiplatelet

Summary



- Aspirin acts by **Irreversible** inhibition of COX1 and COX2 (non- selective)

- Aspirin main actions and uses are:

  1- Antiplatelet at dose of 75-150 mg

  2- Analgesic antipyretic at the dose of 325 mg tablet (1- 2 tablet/ 6 hours)

  3- Anti-Inflammatory at a dose > 4 gm /day

  4- Counter-irritant in Arthritis and Keratolytic (local use)

SUGGESTED TEXTBOOKS



1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.

Thank You